

REVIEWS

Evaluation of Left Ventricular Function by Radionuclide Angiography During Exercise in Normal Subjects and in Patients With Chronic Coronary Heart Disease

ABDULMASSIH S. ISKANDRIAN, MD, FACC, A-HAMID HAKKI, MD, FACC,
NICHOLAS L. DePACE, MD, BRUNO MANNO, MD, BERNARD L. SEGAL, MD, FACC

Philadelphia, Pennsylvania

Radionuclide angiography permits evaluation of left ventricular performance during exercise. There are several factors that may affect the results in normal subjects and in patients with chronic coronary heart disease. Important among these are the selection criteria: age, sex, level of exercise, exercise end points, ejection fraction at rest and effects of pharmacologic agents. An abnormal ejection fraction response to exercise is not a specific

marker for coronary heart disease but may be encountered in other cardiac diseases.

In addition to the diagnostic considerations, important prognostic data can be obtained. Further studies are needed to determine the prognostic implications of anatomic findings versus the functional abnormalities induced by exercise in patients with coronary artery disease.

For the most part, previous studies have relied on contrast angiography to assess global and regional left ventricular function. These studies, performed generally at rest, have provided a wealth of information concerning left ventricular ejection fraction, wall motion, volumes and pressure-volume relation in normal subjects and in patients with cardiovascular disease.

Radionuclide Angiography During Exercise

The precise role of exercise echocardiography in evaluation of left ventricular function is not yet clear, but at the present time radionuclide angiography is the method of choice for assessing cardiac performance during exercise. This review will focus only on left ventricular function during exercise in normal subjects and in patients with chronic coronary heart disease. The radionuclide-derived measurements are listed in Table 1.

Technical considerations for measuring ventricular function and volume are beyond the scope of this presentation

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Address for reprints: Abdulmassih S. Iskandrian, MD, Likoff Cardiovascular Institute, Hahnemann University and Hospital, 230 North Broad Street, Philadelphia, Pennsylvania 19102.

(1-10). Similarly, other interesting aspects of radionuclide scintigraphy (such as regurgitant index, phase imaging, regional ejection fraction and regional stroke volume) will not be discussed because they have not been adequately examined during exercise or have not been widely used. The readers are referred to excellent reports on these subjects (11-19).

Dynamic versus isometric exercise. Exercise can be either isometric or dynamic. Dynamic exercise can be performed in the supine or the upright position. Isometric exercise using a handgrip, although easier to perform, is much less commonly used than dynamic exercise. Previous studies (20-24) show that handgrip exercise increases the heart rate and systolic blood pressure in normal subjects and patients with coronary artery disease. In normal subjects, there is also a decrease in left ventricular end-diastolic volume, end-systolic volume and end-diastolic pressure, although the ejection phase indexes change very little. In patients with coronary artery disease, there is an increase in end-systolic volume and end-diastolic pressure, but a decrease in end-diastolic volume. The ejection phase indexes either decrease or remain unchanged.

Peter and Jones (25) found that the ejection fraction did not change with handgrip exercise in 20 patients with coronary heart disease, although an abnormal ejection fraction response was elicited with dynamic exercise in nine of the

patients. Wall motion abnormalities were induced during handgrip exercise in only 45% of the patients. Assessment of the regional ejection fraction image may enhance the detection of coronary artery disease compared with wall motion assessment (17,18).

Effect of Body Position on Exercise Left Ventricular Performance

Both the Frank-Starling mechanism and an increase in contractility play roles in modulating left ventricular performance during exercise. Previous studies (26-40) show that left ventricular end-diastolic volume, end-diastolic pressure, pulmonary capillary wedge pressure, cardiac output and stroke volume are lower in the erect position than in the supine position. During exercise in the erect position, cardiac index and stroke volume increase in association with a slight increase in left ventricular end-diastolic pressure and pulmonary capillary pressure.

At a low or moderate level of supine exercise the heart rate increases to augment the cardiac output, whereas at maximal exercise, there is also an increase in end-diastolic and stroke volume. Furthermore, in the supine position, with the leg lifting necessary to perform exercise studies, there is a slight increase in end-diastolic volume above the control measurements with the legs in the supine position. Therefore, further changes in end-diastolic volume during supine exercise may not be apparent. On the other hand, blood pooling reduces the end-diastolic volume at rest in the upright position. During upright exercise, the end-diastolic volume increases but may remain lower than the end-diastolic volume at peak supine exercise.

Changes in Left Ventricular Function During Exercise in Normal Subjects

The most widely used radionuclide indexes for evaluating left ventricular performance during exercise are changes in ejection fraction, volumes and wall motion (Table 1).

The increase in cardiac output during exercise in normal subjects depends on increases in heart rate and stroke volume. The increase in stroke volume could be mediated by several mechanisms: 1) a decrease in end-systolic volume with no change in end-diastolic volume; 2) an increase in end-diastolic volume with no change in end-systolic volume; 3) an increase in both end-diastolic volume and end-systolic volume (however, the increase in end-diastolic volume is greater than the increase in end-systolic volume); and 4) an increase in end-diastolic and a decrease in end-systolic volume. All four mechanisms may result in an increase in ejection fraction, which is the ratio of stroke volume to end-diastolic volume. Normal subjects show an increase of at

Table 1. Radionuclide Angiographic Derived Measurements

Left Ventricle	
A. Systolic function	
1. Ejection fraction	
2. End-diastolic and end-systolic volumes	
3. Systolic ejection rate	
4. Wall motion	
5. End-systolic pressure/end-systolic volume ratio	
6. Functional images such as the phase image, stroke volume image and regional ejection fraction image	
B. Diastolic function such as peak diastolic filling rate, filling fraction and time to peak filling rate	
Right Ventricle	
1. Ejection fraction	
2. End-diastolic and end-systolic volumes	
3. Wall motion	
Other	
1. Pulmonary blood volume	
2. Regurgitant index	
3. Intracardiac shunt detection and quantitation	

least 5% in ejection fraction during exercise (compared with rest). This change in ejection fraction has been widely used to characterize normal versus abnormal response to exercise (Fig. 1) (41-50). The incidence of falsely abnormal results (< 5% increase in ejection fraction) in apparently normal subjects varies considerably in different studies (Table 2).

Factors Affecting Ejection During Exercise

Selection criteria. The definition of a normal population is important. In some series, the presence of normal coronary angiograms was required to define the normal group. In others, historic and electrocardiographic criteria alone were used. Even when the angiographic data are used, mild coronary artery disease (< 50% or < 70% diameter narrowing, depending on the definition for significant obstruction) may be present in some subjects. The presence of other forms of cardiac disease may explain the abnormal results in a few apparently normal subjects.

Table 2. Factors That May Affect Ejection Fraction Response to Exercise in Normal Subjects

Selection criteria
Age
Sex
Heart rate at rest
Ejection fraction at rest
Level of exercise
Type of exercise

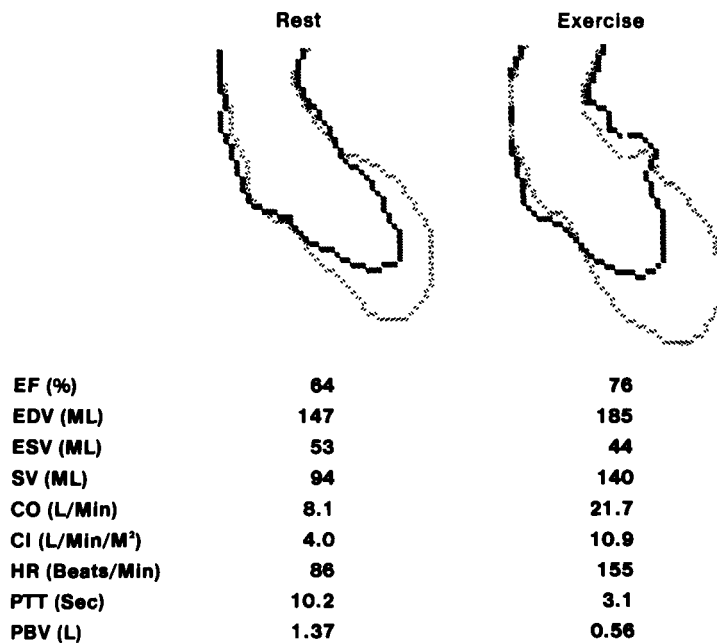


Figure 1. First pass radionuclide ventriculograms obtained at rest and during exercise in a normal subject. The images show superimposed end-diastolic (**light**) and end-systolic (**dark**) perimeters. CI = cardiac index; CO = cardiac output; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HR = heart rate; PBV = pulmonary blood volume; PTT = mean pulmonary transit time; SV = stroke volume.

The presence of symptoms may also be important in defining the exercise response. Thus, Berger et al. (49) found that 12 of 31 patients with chest pain and ischemic changes on electrocardiography had abnormal ejection fraction responses to exercise although the coronary angiograms showed normal results. Similar results have been reported by others (47).

Age. Age may be important. The normal group in some studies consisted of young volunteers, whereas in most other studies the patients were older, generally those referred for cardiac catheterization for complaints of chest pain but who were found subsequently to have normal coronary vessels. Port et al. (41) found a high incidence of abnormal exercise ejection fraction responses in apparently healthy subjects older than 65 years, although the coronary anatomy was not defined in these subjects.

Sex. Sex may also be an important factor. Most exercise data are derived from a predominantly male population. Jones et al. (51) reported that abnormal ejection fraction responses during exercise are more common in normal women than in normal men. The exact reasons are not clear, but perhaps the usual exercise protocol is more strenuous for women than men and, therefore, more gradual exercise in women may yield a lower incidence of false positive results. Foster et al. (45) studied nine young athletes and found that sudden strenuous exercise decreased the ejection fraction, but that more gradual exercise increased the ejection fraction.

Level of exercise. In some instances, the exercise may be inadequate (submaximal) to demonstrate hemodynamic changes. Serial measurements of the ejection fraction during supine exercise have shown gradual increments in ejection fraction as the level of exercise is increased (52). In addition, there is an overshoot phenomenon in the early recovery

period (53), that is, a further increase in ejection fraction soon after termination of exercise over the ejection fraction at peak exercise. Thus, terminating exercise at an early stage because of lack of motivation, lack of familiarity with the exercise protocol or symptoms that are not cardiac in origin (leg fatigue or general fatigue) may evoke abnormal ejection fraction responses in some normal subjects.

Heart rate and ejection fraction at rest. In other patients, anxiety produces sinus tachycardia at rest. In these subjects, the change in ejection fraction from rest to exercise may be misleading because the measurement obtained at rest may, in fact, be closer to the exercise measurement than the basal ejection fraction. Some normal subjects, despite a normal heart rate at rest, have a high (greater than 70%) ejection fraction at rest. In these subjects, the end-systolic volume at rest may approach the lowest possible volume. If the end-diastolic volume does not increase during exercise, then the ejection fraction may fail to increase by more than 5% because the end-systolic volume cannot decrease further. Therefore, the arbitrary use of 5% or more to define a normal response may not be valid in subjects with a hyperkinetic left ventricle at rest.

Reliability and reproducibility of the method. The end-diastolic volume either does not change or increases slightly during supine or upright exercise in normal subjects, whereas the end-systolic volume decreases with resultant increases in stroke volume and ejection fraction (Fig. 1). The end-systolic volume may increase slightly or remain unchanged in a few normal subjects, but in these patients the increase in end-diastolic volume is more than the increase in end-systolic volume, with resultant increases in stroke volume and ejection fraction (41-53). These small increments in the end-systolic volume in a few normal subjects may be

within the range of reproducibility of the technique. It is important, therefore, for each laboratory involved in volume measurements to establish the reliability and reproducibility of the method in comparison with contrast angiography, and also to establish the range of normal responses during exercise.

Training effect. Left ventricular performance during exercise may be modified by training. Rerych et al. (42) found that intensive training resulted in a decrease in ejection fraction and an increase in end-diastolic volume at rest. There was a further increase in end-diastolic volume during exercise. The heart rate and ejection fraction at peak exercise were similar before and after training. These results indicate that cardiac performance can be enhanced by ventricular dilation.

Bar-Shlomo et al. (46) compared the performance of endurance-trained athletes with those of normal sedentary subjects and found that the end-diastolic volume increased in the sedentary group during exercise, but in the athletes there was no change. The athletes had a greater decrease in the end-systolic volume during exercise. Thus, the untrained normal subjects responded to supine exercise by increasing the end-diastolic volume, whereas the trained athletes responded with a decrease in end-systolic volume. The apparent difference between these results and those of Rerych et al. (42) may be explained by the types of exercise: upright in the study of Rerych et al. (42) and supine in the study of Bar-Shlomo et al. (46).

Left Ventricular Performance During Exercise in Patients With Coronary Artery Disease

Role of Myocardial Ischemia

Myocardial ischemia in patients with coronary artery disease (as a result of an imbalance in the oxygen demand-supply ratio) results in deterioration in left ventricular performance, as manifested by regional wall motion abnormalities and abnormalities in ejection fraction and volumes. Although there are other methods for inducing myocardial ischemia, dynamic exercise testing appears to be more effective in eliciting hemodynamic abnormalities.

In general, in patients with coronary artery disease and normal rest left ventricular function, exercise ventricular function is abnormal unless myocardial ischemia was not produced or the area of the ischemia was small. On the other hand, in patients with coronary artery disease and abnormal rest left ventricular performance, exercise function will depend on the extent of scar tissue and the presence or absence of exercise-induced ischemia. Thus, exercise evaluation in such patients may provide prognostic rather than diagnostic data, because the diagnosis may already have been suspected from the rest studies.

Criteria for abnormal response to exercise. The sensitivity of radionuclide ventriculography in detecting coronary artery disease depends to a certain degree on the criteria used for defining an abnormal response (3,4,51-61). The two most commonly used criteria are failure of the ejection fraction to increase by at least 5% during exercise and the presence of exercise-induced wall motion abnormalities (Fig. 2). In some studies (51-61) changes in ventricular volume during exercise are used as independent variables to define an abnormal response. In patients with an abnormal rest ejection fraction or with wall motion abnormalities at rest, the criteria for sensitivity generally have been expanded; these include not only the criteria mentioned but also rest abnormalities, because these abnormalities are likely to be the manifestations of coronary artery disease. Others (62,63) have included the change in the ratio of systolic blood pressure to the end-systolic volume during exercise, and have found that combining the change in ejection fraction, wall motion and pressure-volume relation enhances the detection of coronary artery disease. Others (64-66) have included changes in blood volume to define an abnormal response.

Factors Affecting Ventricular Exercise Performance

The factors that may affect left ventricular performance during exercise in patients with coronary artery disease are listed in Table 3.

Severity and extent of coronary artery disease. Patients with more severe, extensive coronary artery disease are more likely to have abnormal exercise results than patients with single vessel disease (4). These data are comparable with those obtained from exercise electrocardiographic and exercise thallium imaging studies; therefore, the sensitivity for detecting coronary artery disease is lower in patients with single vessel disease than in those with multivessel disease (67).

The change in ejection fraction during exercise is usually more marked in patients with multivessel disease than in those with single vessel disease, but there is considerable variation within each group (Fig. 3). Gibbons et al. (68) studied 281 patients with coronary artery disease with normal rest ventricular function and found that 81% of these patients showed abnormal ejection fraction responses to exercise. The extent of coronary artery disease was only one of the variables that affected the change in ejection fraction with exercise. Other factors were not related to the extent of coronary artery disease.

Wide variation in exercise left ventricular performance has also been reported in patients with single vessel disease (54). These observations are consistent with findings of investigators using exercise thallium-201 imaging (69); the mean size of ischemic myocardium is greater in patients with multivessel disease than in patients with single vessel disease. However, there is considerable variation within

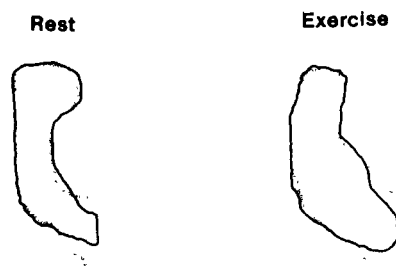


Figure 2. First pass radionuclide ventriculograms obtained at rest and during exercise in a patient with severe coronary artery disease. The format is the same as in Figure 1. There is a decrease in ejection fraction during exercise, with new wall motion abnormalities. BP = blood pressure; MTT = mean transit time; other abbreviations as in Figure 1.

HR (beats/min)	68	110
BP (mmHg)	135/85	180/100
EF (%)	74	45
EDV (ml)	120	208
ESV (ml)	31	115
SV (ml)	89	96
CO (L/min)	6.0	10.3
CI (L/min/M ²)	3.2	5.5
MTT (Sec)	6.0	3.7
PBV (L)	.32	.63

each group. This variation may be partially explained by the severity and location of the obstructions and the effects of collateral circulation. When the extent of coronary artery disease is quantitated using a scoring system that takes these factors into consideration, an inverse correlation between the coronary artery disease score and the exercise ejection fraction can be found (70). Therefore, there may be an advantage in quantitating the extent of coronary artery disease rather than reporting the results as single vessel or multivessel disease.

Level of exercise. The level of exercise and exercise end points also affect left ventricular function during exercise. Brady et al. (60) and Berger et al. (59) found that abnormal ejection fraction responses during exercise were more frequent in patients with coronary artery disease who had chest pain or ST depression during stress than in patients who had inadequate exercise. Upton et al. (57) exercised 25 patients with coronary artery disease at two levels of exercise: submaximal, in which no patient developed ST segment depression or complained of angina, and maximal, in which all patients had either angina or ST segment depression. Abnormal ejection fraction responses were encoun-

tered in 18 of 25 patients during submaximal exercise and in all patients during maximal exercise. Other investigators (52) found that the incidence of abnormal ejection fraction response to exercise was similar in patients who experienced angina during exercise to the incidence in patients who did not. By and large, our experience is in agreement with the latter results.

Left ventricular function at rest. Ejection fraction at rest may effect a change in ejection fraction during exercise. Several studies (58,71) have shown that in patients with coronary artery disease and severely depressed left ventricular ejection fraction at rest, the ejection fraction during exercise may increase by at least 5%. These data do not support the contention of Schoolmeester et al. (72), who suggested that the response of ejection fraction to exercise in patients with severe left ventricular dysfunction may help differentiate patients with ischemic cardiomyopathy from those with primary cardiomyopathy.

Methodologic factors. During the early recovery period (53) there is an overshoot phenomenon in patients with coronary artery disease, as in normal subjects, and therefore it is important to measure the ejection fraction at peak exercise. Otherwise, incorporation of data from the early recovery period may produce falsely high results.

Overestimation of the severity of coronary artery disease by angiography may be responsible for some false-negative results. The effects of other factors listed in Table 3 will be discussed later.

The changes in end-diastolic volume and end-systolic volume during exercise are less sensitive markers than change in ejection fraction in detecting coronary artery disease (73). One point concerning volume changes during exercise with the gated method should be stressed in the light of the recent findings by Konstam et al. (74). These investigators found

Table 3. Factors That May Affect Ejection Fraction Response During Exercise in Patients With Coronary Artery Disease

Severity and extent of coronary artery disease
Left ventricular function at rest
Previous myocardial infarction
Effect of training
Effect of pharmacologic agents
Level of exercise

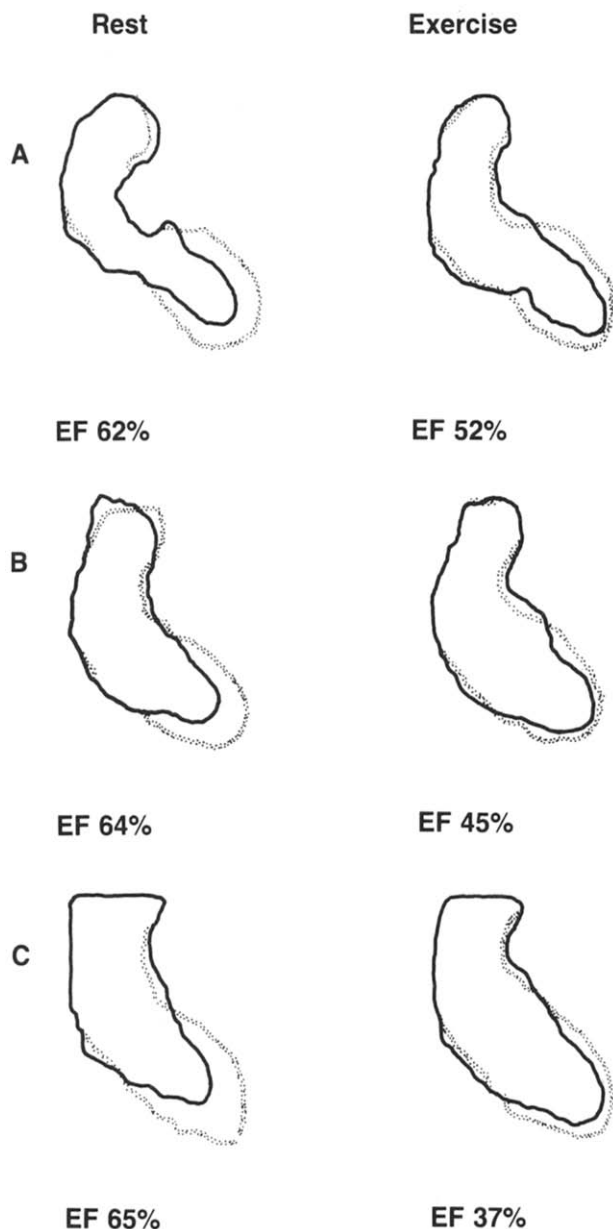


Figure 3. Radionuclide ventriculograms obtained at rest and during exercise in three patients with three vessel coronary artery disease, showing variable degrees of exercise-induced left ventricular dysfunction manifested by a decrease in ejection fraction (EF) and wall motion abnormalities during exercise. The change in ejection fraction (EF) from rest to exercise is greater in **panel C** than in **B** and **A**.

that during exercise there is an increase in blood radioactivity, presumably because of the release of labeled red blood cells from the spleen; thus, changes in radioactivity in the left ventricle may not be due to changes in volumes. Therefore, if volume measurements are performed during exercise, blood activity should also be measured.

Exercise-Induced Wall Motion Abnormalities

The incidence of exercise-induced wall motion abnormalities, in the form of either new wall motion abnormalities or worsening of existing abnormalities, varies considerably in different series. Thus, Borer et al. (52) found that 94% of 63 patients with coronary artery disease showed regional dysfunction during exercise. However, Jones et al. (51) found exercise-induced wall motion abnormalities in only 56% of their patients with coronary artery disease. The lower incidence of wall motion abnormalities as compared with ejection fraction changes during exercise in patients with coronary artery disease may be attributed to the subjective nature of analysis of wall motion and to the fact that wall motion assessment may be available in only one projection. Biplane studies or studies performed in two different projections may increase the yield of wall motion abnormalities.

Effect of Training

The relative contribution of central and peripheral adaptation in producing the training effect in patients with coronary artery disease has been debated (75-87). Enhanced oxidative capacity in trained muscles and an increase in the arterial-venous oxygen difference are indicators that peripheral adaptation occurs (78,79). Previous studies showed that training did not change collateral circulation, scintigraphic findings or rest left ventricular function. Training also had no effect on coronary sinus blood flow or left ventricular oxygen consumption during exercise (80-82).

Verani et al. (85) evaluated the effects of 12 week training periods on left ventricular function and perfusion in 16 patients with coronary artery disease. Exercise tolerance improved after training. However, there was no improvement in left ventricular reserve function, as assessed by wall motion and ejection fraction during exercise at the same rate-pressure product (heart rate \times blood pressure) as that before training. Similarly, there was no improvement in the exercise myocardial perfusion pattern after training. Thus, improvement in these patients resulted from factors other than improved pump performance or perfusion. Similar results were reported by Cobb et al. (86).

Tubau et al. (87) found that training had no effect on mean exercise ejection fraction in 17 patients who entered the training program more than 3 months after acute myocardial infarction, although 6 patients showed improvement and 2 patients showed deterioration. The perfusion pattern was improved in 5 patients and deteriorated in 1 patient, but the changes in perfusion and function were not concordant. It may be concluded, therefore, that the effect of training on left ventricular function may depend on the patient population and the time elapsed since myocardial infarction. In general, however, changes in pump function and perfusion are not the main reasons for symptomatic improvement.

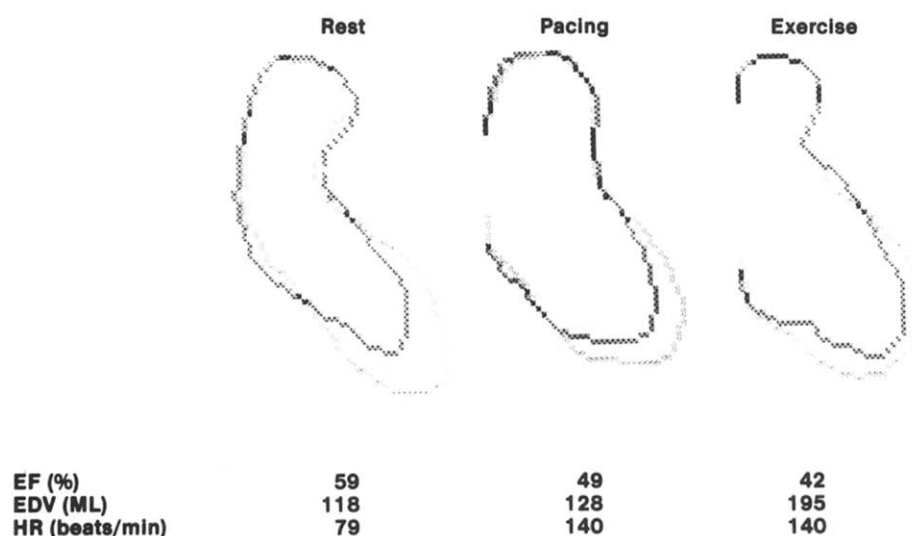


Figure 4. Radionuclide ventriculograms obtained at rest in the control state, during rapid atrial pacing and during upright dynamic exercise in a patient with coronary artery disease. The heart rate (HR) was the same during pacing and exercise, but the depression in ejection fraction (EF) was more marked during exercise than during pacing. Also, the end-diastolic volume (EDV) increased more with exercise than with pacing.

Diastolic Left Ventricular Function

The discussion so far has focused on determining systolic left ventricular function. It is known that ischemic heart disease affects diastolic and systolic function of the left ventricle. Radionuclide ventriculography has been used to assess the diastolic function of the left ventricle (88-91). The two most common measurements used have been the peak filling rate and the time to peak filling rate (89). High-frequency framing rates are required to obtain these measurements.

Peak filling rate. The diastolic function is abnormal at rest in many patients with coronary artery disease, irrespective of the rest ejection fraction and the presence or absence of prior infarction (89). However, substantial overlap exists between normal subjects and patients with coronary artery disease except when left ventricular dysfunction is severe and apparent clinically. Thus, the usefulness of this isolated measurement in detecting coronary disease is limited in any individual patient. Furthermore, an abnormal peak filling rate is not a specific finding as it may be seen in cardiac diseases other than coronary artery disease (91). The peak filling rate increases during exercise in normal subjects and patients with coronary artery disease, although the change is less marked in patients with coronary artery disease (91). It appears that the diastolic indexes are less sensitive than the systolic indexes during exercise in identifying patients with coronary artery disease (90).

Effect of Pharmacologic Agents on Left Ventricular Performance During Exercise

Radionuclide ventriculography provides an ideal technique for evaluating the effects of pharmacologic agents on cardiac performance at rest and during exercise. Several

antianginal, antiarrhythmic and vasodilator drugs have been studied. It is important to understand their effects on cardiac performance so as to understand not only their mode of action but also the way in which they may modify left ventricular response to exercise; this in turn may affect the diagnostic accuracy of these studies in patients with coronary artery disease (92-98).

Nitroglycerin

Slutsky et al. (99) compared the effects of sublingual nitroglycerin with those of nitroglycerin paste on left ventricular function and volume during supine exercise. They found that both agents decreased end-diastolic volume and end-systolic volume at rest. The end-diastolic volume increased during supine exercise after sublingual nitroglycerin but remained below the control measurement. However, with nitroglycerin paste, there was no change in end-diastolic volume during exercise. The ejection fraction improved during exercise with both forms of nitrates. Thus, both forms of nitroglycerin improved left ventricular function during exercise; however, the effect of paste on volumes was sustained, whereas that of sublingual nitroglycerin was transient. The decrease in the end-diastolic volume may explain the beneficial effects of nitroglycerin by decreasing wall tension.

In another study (100), nitroglycerin was found to improve left ventricular function, both at rest and during exercise, in patients with coronary artery disease. Sorenson et al. (101) examined the effect of 0.6 mg of nitroglycerin given sublingually on left ventricular function in nine normal subjects, both at rest and during supine exercise. The end-diastolic volume decreased initially and then increased to the pre-drug level at maximal exercise; this is presumably

because ventricular impedance decreases to a low value during exercise in normal subjects, and therefore nitroglycerin will have little further effect.

Propranolol

The beneficial antianginal effect of propranolol appears to be due to its beta-receptor blockade action, which decreases the heart rate and rate-pressure product at comparable work loads. Therefore, the myocardial oxygen demand at comparable work loads is lower with propranolol therapy, and ischemic dysfunction is absent or not as severe.

The effects of propranolol on left ventricular function at rest and during exercise have been evaluated in both normal subjects and patients with coronary artery disease. The effects of propranolol on function at rest have been variable. Port et al. (102) reported that propranolol decreased ejection fraction in normal subjects at rest and during upright exercise at comparable work loads. However, when the hemodynamics were examined at comparable heart rates, they were not significantly different. Thus, in normal subjects, the hemodynamic effects of propranolol are due to changes in the heart rate.

On the other hand, Marshall et al. (103) found that propranolol had no effect on rest and exercise left ventricular function with intermediate doses of propranolol (160 mg/day), whereas higher doses produced a decrease in ejection fraction at equivalent heart rate and blood pressure products and at peak exercise. Propranolol improved regional and global performance of the left ventricle in patients with coronary artery disease who manifested ischemic dysfunction during exercise without propranolol therapy, but no significant effect was noted in the absence of such ischemic changes (103-105).

Implications. The implications of these studies may be summarized as follows: in patients with coronary artery disease who have angina or ST depression during exercise despite propranolol therapy, exercise left ventricular studies should be meaningful in determining the presence or absence of coronary artery disease. However, when patients with suspected coronary artery disease on propranolol therapy do not have angina or ST depression or fail to achieve an adequate heart rate during exercise, a normal exercise ejection fraction response may not be a valid criterion to exclude the possibility of coronary artery disease. In such patients, it may be important to discontinue the medication and repeat the exercise studies.

Comparison Between Propranolol and Verapamil

Calcium channel blocking agents have been used in patients with coronary artery disease and have provided symptomatic improvement comparable with that achieved with propranolol. Johnson et al. (106) compared propranolol with verapamil in patients with coronary artery disease and stable

angina pectoris. They found that both drugs significantly alleviated the symptoms without significant effects on left ventricular ejection fraction at rest and during exercise. As expected, the heart rate was lower at peak exercise during propranolol therapy than during control or verapamil therapy. The peak exercise heart rate was also slightly lower than the control rate during verapamil therapy. The end-diastolic volume increased during exercise in the control study, but did not change during propranolol or verapamil therapy. The end-systolic volume did not change with exercise in the control study and during propranolol therapy, but increased slightly during verapamil therapy.

Josephson et al. (107) found that verapamil, 400 mg/day, or propranolol, 320 mg/day, did not affect the rest ejection fraction or wall motion. Both drugs attenuated the increase in heart rate with exercise at a comparable work load, although the attenuation was less marked with verapamil than with propranolol. The ejection fraction decreased from rest to exercise in the control study, but did not change during propranolol or verapamil therapy. Both drugs resulted in symptomatic improvement during exercise.

These results are different from those of Bonow et al. (108), who found that verapamil decreased the ejection fraction at rest, but increased the peak filling and decreased the time to peak filling rate; the latter two indexes reflect the diastolic function of the left ventricle. During exercise, the ejection fraction did not change, but the peak filling rate increased and the time to peak filling rate decreased with verapamil therapy. On the other hand, propranolol had no effect on the ejection fraction, peak filling rate or the time to peak filling rate, either at rest or during exercise. Thus, it appears that one reason for symptomatic improvement with verapamil is the improved diastolic function of the left ventricle.

Tan et al. (109) found that verapamil did not affect the ejection fraction at rest but improved the ejection fraction during exercise. There was less increase in the end-systolic volume with verapamil therapy than with placebo. Improvement in exercise left ventricular function with propranolol or verapamil therapy has also been reported by Sadick et al. (110).

In patients with variant angina, neither verapamil nor nifedipine was found to change the ejection fraction, end-diastolic volume and end-systolic volume at rest or during exercise at comparable work loads when compared with placebo (111).

In summary, both verapamil and propranolol improved exercise tolerance and symptoms in patients with angina; they had no great effect on rest ejection fraction, but did improve exercise ventricular function, especially if ischemia was present during exercise before treatment. Although the chief benefits of propranolol therapy appear to be a decrease in myocardial oxygen demand, the beneficial effects of verapamil may include, in addition, improving diastolic func-

tion of the ventricle and, possibly, preventing exercise-induced spasm in some patients.

Other Forms of Stress Testing

In some patients, an adequate exercise study cannot be obtained because of other associated conditions, such as peripheral vascular disease or neuromuscular disease. In these patients other techniques, such as the cold pressor test (112), dipyridamole infusion (113) or atrial pacing (114), may be used. In general, these tests result in fewer hemodynamic abnormalities than those that occur during dynamic exercise. We obtained radionuclide angiograms in eight patients with coronary artery disease during upright exercise and during atrial pacing. The heart rates in both intervention studies (exercise and pacing) were identical in each patient; pacing produced fewer hemodynamic abnormalities than exercise (Fig. 4).

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